CLAIMS

What is Claimed Is:

1. A compound comprising a megalin-binding moiety conjugated to an agent of interest.

2. The compound of claim 1, wherein said agent is selected from the group consisting of a therapeutic agent, a diagnostic agent, a marker of a disease of the central nervous system (CNS), a labeled monoclonal antibody which binds a marker of a CNS disorder.

3. The compound of claim 2, wherein said therapeutic agent is selected from the group consisting of a protein, a cytotoxic chemotherapeutic agent, a protein nucleic acid, an siRNA molecule, an antisense molecule, and an expression construct comprising a nucleic acid that encodes a therapeutic protein of interest.

4. The compound of claim 1, wherein said megalin binding moiety and said agent of interest are directly linked to each other.

5. The compound of claim 1, wherein said megalin binding moiety and said agent of interest are linked through a linker.

6. The compound of claim 5, wherein said linker is a peptide linker.

7. The compound of claim 1, wherein said megalin binding moiety is a moiety that is transcytosed in vivo.

8. The compound of claim 1, wherein said megalin binding moiety is selected from the group consisting of RAP, thyroglobulin, lipoprotein

lipase, lactoferrin, apolipoprotein J/clusterin, apolipoprotein B, apolipoprotein E, tissue type plasminogen activator, uPA, PAI-1, vitamin D-binding protein, vitamin A/retinol-binding protein, β2-microglobin, α1-microglobulin, vitamin B12/cobalamin plasma carrier protein, transcobalamin (TC)-B12, PTH, insulin, EGF, prolactin, albumin, apo H, transthyretin, lysozyme, cytochrome-c, α-amylase, and Ca2+, and aprotinin.

9. The compound of claim 8, wherein said megalin binding moiety is receptor associated protein.

10. A chimeric molecule for transcytotic delivery into the brain across the blood-brain barrier, said chimeric molecule comprising a megalin ligand conjugated to an active agent to be delivered across the blood-brain barrier by transcytosis, wherein said megalin ligand facilitates transport of said chimeric molecule across the blood-brain barrier.

11. A chimeric molecule for delivery into the brain by transcytosis across the blood-brain barrier, said chimeric molecule comprising an LRP ligand conjugated to an active agent to be delivered across the blood-brain barrier by transcytosis, wherein said LRP ligand binds preferentially to megalin as compared to LRP1.

12. The compound of any of claims 1 through 8, or the chimeric molecule of any of claims 10 or 11, wherein said agent of interest is bound to the C-terminus of the megalin binding moiety.

13. The compound of any of claims 1 through 8, or the chimeric molecule of any of claims 10 or 11, wherein said megalin-binding moiety and said agent of interest are each a protein and megalin-binding moiety is bound to the N-terminus of the agent of interest.

14. A pharmaceutical composition comprising a compound of any of claims 1 through 8, or a chimeric molecule of any of claims 10 or 11 in a pharmaceutically acceptable carrier, diluent or excipient.

15. A pharmaceutical composition comprising a compound of claim 12 in a pharmaceutically acceptable carrier, diluent or excipient.

16. A pharmaceutical composition comprising a compound of claim 13 in a pharmaceutically acceptable carrier, diluent or excipient.

17. A method of delivering an agent into the central nervous system of an animal comprising administering said animal said agent conjugated to a megalin binding moiety, wherein the transport of said agent conjugated to said megalin-binding moiety across the blood brain barrier of said animal is greater than the transport of said agent in the absence of conjugation to said megalin binding moiety.

18. A method of increasing transcytosis of an agent, comprising conjugating said agent to a megalin-binding moiety, wherein transcytosis of said agent when conjugated to said megalin- binding moiety is greater than the transcytosis of said agent in the absence of said conjugation.

19. A method of treating a disorder in a mammal comprising administering to said animal a therapeutic agent conjugated to a megalin binding moiety.

20. The method of claim 19, wherein said disorder is a disorder of the CNS.

21. The method of claim 20, wherein said disorder is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis, Amylotrophic Lateral Sclerosis, and a central nervous system cancer.

22. The method of claim 21, wherein said disorder is a central nervous system cancer and said agent is a cancer chemotherapeutic agent.

23. A method of delivering a therapeutic enzyme to a lysosomal compartment in a cell expressing megalin, comprising contacting said cell with a composition comprising said therapeutic enzyme conjugated to a megalin-binding moiety, wherein the uptake of said therapeutic enzyme into the lysosomal compartment of said cell is mediated through megalin present on the surface of said cell.

24. A method of treating a lysosomal storage disease (LSD) in a subject comprising administering to said subject a composition comprising a megalin-binding moiety conjugated to a therapeutic agent used in the treatment of said LSD, in an amount effective to ameliorate the symptoms of said LSD.

25. The method of claim 24, wherein said therapeutic agent is an enzyme deficient in said LSD.

26. The method of claim 24, wherein said LSD is selected from the group consisting of lysosomal storage disease is selected from the group consisting of aspartylglucosaminuria, cholesterol ester storage disease, Wolman disease, cystinosis, Danon disease, Fabry disease, Farber lipogranulomatosis, Farber disease, fucosidosis, galactosialidosis types I/II, Gaucher disease types I/II/III, Gaucher disease, globoid cell leukodystrophy, Krabbe disease, glycogen storage disease II, Pompe disease, GM1-gangliosidosis types I/II/III, GM2-gangliosidosis type I, Tay Sachs disease,

GM2-gangliosidosis type II, Sandhoff disease, GM2-gangliosidosis, α-mannosidosis types I/II, β-mannosidosis, metachromatic leukodystrophy, mucolipidosis type I, sialidosis types I/II mucolipidosis types II /III I-cell disease, mucolipidosis type IIIC pseudo-Hurler polydystrophy, mucopolysaccharidosis type I, mucopolysaccharidosis type II, Hunter syndrome, mucopolysaccharidosis type IIIA, Sanfilippo syndrome, mucopolysaccharidosis type IIIB, mucopolysaccharidosis type IIIC, mucopolysaccharidosis type IIID, mucopolysaccharidosis type IVA, Morquio syndrome, mucopolysaccharidosis type IVB Morquio syndrome, mucopolysaccharidosis type VI, mucopolysaccharidosis type VII, Sly syndrome, mucopolysaccharidosis type IX, multiple sulfatase deficiency, neuronal ceroid lipofuscinosis, CLN1 Batten disease, Niemann-Pick disease types A/B, Niemann-Pick disease, Niemann-Pick disease type C1, Niemann-Pick disease type C2, pycnodysostosis, Schindler disease types I/II, Schindler disease, and sialic acid storage disease.

27. The method of claim 25, wherein the agent is selected from the group consisting of aspartylglucosaminidase, acid lipase, cysteine transporter, Lamp-2, α-galactosidase A, acid ceramidase, α-L-fucosidase, β-hexosaminidase A, GM2-activator deficiency, α-D-mannosidase, β-D-mannosidase, arylsulfatase A, saposin B, neuraminidase, α-N-acetylglucosaminidase phosphotransferase, phosphotransferase γ-subunit, L-iduronidase, iduronate-2-sulfatase, heparan-N-sulfatase, α-N-acetylglucosaminidase, acetylCoA:N-acetyltransferase, N-acetylglucosamine 6-sulfatase, galactose 6-sulfatase, β-galactosidase , N-acetylgalactosamine 4-sulfatase, hyaluronoglucosaminidase, multiple sulfatases, palmitoyl protein thioesterase, tripeptidyl peptidase I, acid sphingomyelinase, cholesterol trafficking, cathepsin K, α-galactosidase B, and sialic acid transporter.

28. The method of claim 24, wherein said composition is a pharmaceutical composition and is administered in an amount effective to decrease the amount of storage granules present in the brain tissue of said mammal.

29. The method of claim 24, wherein said administering comprises intrathecal administration into the central nervous system of the mammal.

30. The method of claim 24, wherein said composition is administered in an amount effective to decrease the amount of storage granules present in the meningeal tissue of said mammal.

31. The method of claim 24, wherein said symptoms are monitored through routine assessment of history, physical examination, echocardiography, electrocardiography, magnetic resonance imaging, polysomnography, skeletal survey, range of motion measurements, corneal photographs, and skin biopsy.

32. The method of claim 26, wherein the disease is mucopolysaccharidosis.

33. The method of claim 32, wherein the disease is mucopolysaccharidosis I.

34. The method of claim 24, wherein said mammal with said lysosomal storage disease demonstrates about 50% or less of a normal α-L-iduronidase activity.

35. The method of claim 28, wherein said pharmaceutical composition is administered at a dose of between about 0.001mg/kg body weight and 0.5 mg/kg body weight of said human α-L-iduronidase administered weekly to a subject suffering from a deficiency thereof.

36. The method of claim 28, wherein said pharmaceutical composition is administered at a dose of between about 0.01 mg/15 cc of CSF to

about 5.0 mg/15 cc of CSF of the mammal of said human α-L-iduronidase is administered weekly to a subject suffering from a deficiency thereof.

37. The method of claim 24, wherein said administering of a megalin-binding moiety conjugated to a therapeutic agent results in normalization of developmental delay and regression in said subject, reduction in high pressure hydrocephalus, reduction in spinal cord compression in said subject, and reduction in number and/or size of perivascular cysts around the brain vessels of said subject.

38. The method of claim 29, wherein said intrathecal administration comprises introducing said pharmaceutical composition into a cerebral ventricle.

39. The method of claim 38, wherein said intrathecal administration comprises introducing said pharmaceutical composition into the lumbar area or the cisterna magna.

40. The method of claim 38, wherein said intrathecal administration is achieved by use of an infusion pump.

41. The method of claim 24, wherein said pharmaceutical composition is intrathecally administered continually over a period of at least several days.

42. The method of claim 24, wherein the mammal is a human.

43. The method of claim 25, wherein said method further comprises inducing antigen specific tolerance prior to the enzyme replacement therapy.

44. The method of claim 43, wherein said antigen specific tolerance comprises administration of an immunosuppressive agent.

45. The method of claim 44, wherein said immunosuppressive agent is cyclosporine A.

46. The method of claim 44, wherein said antigen specific tolerance further comprises administration of an antiproliferative agent.

47. The method of claim 46, wherein the antiproliferative agent is selected from the group consisting of a nucleotide analog or an anti-metabolite.

48. The method of claim 46, wherein the antiproliferative agent is azathioprine.

49. A method of promoting the breakdown of glycosaminoglycan (GAG) in a brain cell of a subject having lysosomal storage disease, said method comprising administering to said subject a pharmaceutical composition comprising an enzyme deficient in said lysosomal storage disease conjugated to a megalin-binding moiety in an amount effective to reduce the amount of GAG present in said brain cell as compared to the amount of GAG present in said cell prior to said administration.

50. The method of claim 49, wherein said brain cell is a neuron.

51. The method of claim 49, wherein said brain cell is a neuroglial cell.

52. The method of claim 49, wherein said brain cell is an ependymal cell.

53. The method of claim 49, wherein said brain cell is a brain cell selected from at least one of the group consisting of neurons, glial cells, microglial cells, astrocytes, oligodendroglial cells, perivascular cells, perithelial cells, meningeal cells, ependymal cells, arachnoid granulation cells, arachnoid membranes, dura mater, pia mater and choroid plexus cells.

54. The method of claim 53, wherein said brain cell is a meningeal cell.

55. The method of claim 49, wherein said subject has high pressure hydrocephalus and said administering reduces the amount of CSF fluid in the meningeal tissue of said subject.

56. The method of claim 49, wherein the number of lysosomal storage granules in said cell are reduced as compared to the number of lysosomal storage granules present in a similar cell in the absence of administration of said conjugate.

57. The method of claim 49, wherein the number of lysosomal storage granules in said cell is reduced as compared to the number of lysosomal storage granules present in a similar cell treated with enzyme alone without conjugation to said megalin-binding moiety.